P070023
Oxiplex®/SP Gel
FzioMed, Inc.

FDA Presenters:

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Orthopaedic and Rehabilitation Devices Panel Meeting

July 15, 2008

PMA Review Team

- Jismi Jose – Lead Review
- Kevin Lee, MD – Clinical Review
- Jack Zhou – Statistical Review
- Sambasiva Arepalli, PhD – Non-Clinical Review
- Jiping Chen, MD, PhD, MPH – Post-Approval Study
- Isatu Bah – BIMO Review
- Jodi Anderson, Emil Wang, Eric Horowitz – Manufacturing Review
- Mary Ann Wollerton – Patient Labeling

FDA Presentation

- Introduction
- Summary of Non-Clinical/Pre-Clinical Studies
- Clinical Study
- Statistical Overview
- Post-Approval Study
- Panel Questions

Rationale for Bringing to Panel

- First-of-a-kind device
- Clinical significance of device
- Interpretation of clinical study results

Proposed Indications for Use

Oxiplex®/SP Gel is intended to be used as a surgical adjuvant during posterior lumbar laminectomy, laminotomy, or discectomy to improve patient outcomes by reducing postoperative leg pain, back pain and neurological symptoms.

(*Panel Question #1)*

Device Description

- Absorbable, clear, viscoelastic gel
- Physical separation of tissues
- Sodium carboxymethylcellulose (CMC) and polyethylene oxide (PEO) in sterile water
- $CaCl_2$ for stability and NaCl for isotonicity
- No animal/bacterial components or color additives
- Single-use sterile kit containing 3mL syringe and applicator

Mechanism of Action

- Applied to operative site coating neural tissue and filling laminectomy/laminotomy site
- Intended to provide physical separation of tissues during healing process
- Designed to clear from body
- Does not require removal operation

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Non-Clinical Studies

Chemical Analyses

- FTIR Analysis
- EtO Testing
- Aldehyde Testing

Physical Analyses

- Contact Angle Measurement
- Viscometry
- Coatability Testing
- SEC-MALS Testing
- Gel Swelling Test

Pre-Clinical Studies

- Microbiology Tests
  - Rabbit Pyrogen Test
  - LAL Test
- Biocompatibility Tests
  - ISO 10993
  - Literature search
- Animal Studies

Animal Studies

- 2-level rabbit laminectomies at L4 and L5*
  - Purpose: to study effect of device on epidural, dural, or perineural adhesion formation
  - Implanted material: different Oxiplex gel and/or film formulations consisting of CMC and PEO**
  - Sacrifice: various time intervals (*e.g.* btw 19-28 days, 6 wks after surgery)
- Results
  - Fewer adhesions in Oxiplex-treated animals

*Some test animals also underwent a discectomy

**Exact formulation used in Oxiplex/SP Gel was not used in these studies

Animal Studies

- Rabbit laparotomy and uterine horns abraded
  - Purpose: to study efficacy of device in reducing adhesions in uterine horn
  - Implanted materials: different Oxiplex gel formulations consisting of CMC and PEO**
  - Sacrifice: 7 days post-surgery
- Results
  - Adhesion formation reduced at gel-treated sites

**Exact formulation used in Oxiplex/SP Gel was not used in this study

Animal Studies

- 2-level rabbit laminectomies at L4 and L5 + dural nicks
  - Purpose: to study efficacy of device in reducing epidural adhesions & effect of device on dural nick
  - Implanted material: **Oxiplex/SP Gel** or different gel and/or film formulations consisting of CMC and PEO
  - Sacrifice: 28 days or 14-15 days post-surgery
- Results
  - Wound healing, including healing of dural nicks, not impaired
  - Fewer adhesions in Oxiplex-treated animals
  - No remanent Oxiplex/SP gel at 28 days

(*Panel Question #2)*

FDA Presentation

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P070023
Clinical Study

Pilot Study
Pivotal Study

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Office of Device Evaluation

Orthopaedic and Rehabilitation Devices Panel Meeting
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Pilot Study Design

- # of sites: 4
- # of subjects in Oxiplex group: 23
- # of subjects in Control group: 12
- Post-Operative
  - Clinical evaluations: 1 and 3 mos
  - ODI and LSOQ evaluations: 1,3, 6 and 12 mos
  - MRI: 3 mos

Indications/Intended Use for Pilot Study

- Indication
  - Reduction of adhesions following lumbar surgery.
- Intended Use
  - Adjunct to surgery during lumbar laminectomy, laminotomy, and discectomy procedures. The device was intended to inhibit the formation of peridural fibrosis and dural adhesions that might otherwise contribute to postoperative radicular pain and/or neurological dysfunction.

Pilot Study Results

- Study not powered to demonstrate statistically significant differences between two groups
- Higher incidence of adverse events (AEs) in Oxiplex group compared to Control group

	Oxiplex (n=23)	Control (n=12)
Leg pain	5 (22%)	1 (8%)
Back pain	6 (26%)	1 (8%)
Muscle spasm	4 (17%)	2 (17%)
Back stiffness	3 (13%)	2 (17%)
Buttock pain	3 (13%)	0 (0%)
Lower extremity pain	5 (22%)	1 (8%)
Post procedural pain	8 (3 5%)	5 (42%)
Incisional pain	8 (3 5%)	5 (42%)
Lower extremity numbness	4 (17%)	1 (8%)
Hypoaesthesia	6 (26%)	1 (8%)
Paresthesia	3 (13%)	0 (0%)
Sensory loss	2 (9%)	1 (8%)
Nausea	8 (35%)	2 (17%)
Vomiting	4 (17%)	1 (8%)
Constipation	3 (13%)	1 (8%)

Pilot Study Results at 12 Months

	Oxiplex		Control		
Variable	N	Mean	N	Mean	p
Change from Baseline					
Leg Pain (LSOQ)	23	40.7	11	46.6	0.532
Symptoms (LSOQ)	22	28.9	11	34.5	0.529
Activity Related Pain Index (LSOQ)	23	0.87	11	0.92	0.904
Functional Disability (LSOQ)	22	23.1	11	25.8	0.780
Weakness in lower Extremity (LSOQ)	23	0.91	11	0.91	0.993
Radiculopathy Score (LSOQ)	23	34.9	11	40.5	0.486
Oswestry Disability Index (ODI)	23	33.1	11	30.8	0.786

P values determined using ANOVA
Note small sample size
LSOQ is a 100 point scale.

MRI Scar Score Analysis

		Oxiplex		Control	
Parameter	Statistics	Reader1	Reader2	Reader1	Reader2
Subjects enrolled at day 90	N	23		11	
Kappa 0.6543(1) 0.6596(2)	N	23	23	10	10
	Median	1.550	1.550	1.775	1.600
	Mean	1.746	1.600	1.640	1.585
	S.E.	1.284	0.1160	0.1536	0.1665
	Min, Max	0.65, 3.25	0.6, 2.70	0.70, 2.25	0.65, 2.25

MRI scores were based on a scale of 0-6, where 0 = None, 1 = 0-5% abnormalities, 2 = 6-25%, 3 = 26-50%, 4 = 5 1-75%, 5 = 76-95%, and 6 = 96-100%.

Indications for Use in Pivotal Study*

Oxiplex®/SP Gel is intended to be used as a surgical adjuvant during posterior lumbar laminectomy, laminotomy, or discectomy to improve patient outcomes by reducing postoperative leg pain, back pain and neurological symptoms.

*Differs from pilot study indications; same as proposed in PMA

Pivotal Study Design

- Prospective, multi-center, randomized, third-party blinded, parallel group study
- Subjects underwent lumbar disc surgery (standard laminectomy, laminotomy, and discectomy)
- Subjects randomized 1:1 intraoperatively, immediately prior to wound closure
  - Oxiplex group: surgery + Oxiplex/SP Gel
  - Control group: surgery
- Subjects and evaluators masked to treatment assignment
- Follow-up assessments conducted at 1, 3, and 6 mos

Pivotal Study Design, Continued

- Study approved for up to 25 sites investigational sites and up to 394 total subjects.
- # of US sites: 29
  - no foreign sites
- Intent-to-Treat (ITT): 352 subjects
  - # of subjects in Oxiplex group: 177
  - # of subjects Control group: 175
- Completed Cases (CC): 334 subjects who completed 6 mos post-surgical follow-up visit

Safety Endpoints

Primary Safety Endpoint

- Evaluation of frequency and severity of AEs, including surgical complications, categorized using MedDRA coding system (Version 7.1)

Secondary Safety Endpoints

- Changes in laboratory results, physical and neurological exam and vital signs throughout the study;
- Re-operations at lumbar level; and
- Use of concomitant therapies.

Effectiveness Endpoints

- Primary Effectiveness Endpoint
  - Improvement in composite leg pain from baseline to follow-up visits (1, 3 and 6 months), as measured by LSOQ
- LSOQ
  - Measures leg pain severity on 6-pt rating scale for each of the 6 questions
  - Calculated composite leg pain severity score ranges from 0 to 100
    - Higher scores indicate higher overall severity of pain
  - Validated through two multicenter studies

Effectiveness Endpoints, Continued

- Secondary Effectiveness Endpoints:
  - Improvements from baseline (follow-up visit score minus baseline score) as measured by LSOQ, through 6 months, in the following order for sequential closed testing:
    1. back pain
    2. leg weakness
    3. physical symptoms
    4. subject satisfaction
    5. disability score
    6. activities of daily living

Changes in Statistical Analysis Plan

- IDE
  - Sponsor proposed a longitudinal analysis of improvement in composite leg pain using GEE, including treatment, time, and baseline level and baseline by treatment interaction in the model.
  - Sponsor provided null and alternative hypotheses:
    - H_0: $\mu_t = \mu_c$ vs. H_a: $\mu_t \neq \mu_c$

Changes in Statistical Analysis Plan, Continued

- Sponsor proposed to analyze primary endpoint with one-tailed t-test after interim analysis. FDA asked sponsor to include all clinically relevant covariates, such as baseline pain score and site, using original analysis plan.
- The sponsor also stated that they would perform a descriptive presentation and multivariate test of the primary hypothesis for leg pain using a GEE model.

Study Success/Failure

- For the primary effectiveness endpoint, the sponsor set the success criteria of the Pivotal Study as an improvement of 15 points in composite leg pain score from baseline at 6 months on 100-pt LSOQ scale.
- FDA Advisory: In order for study to be considered a success, there should be a statistical significance, as well as a clinically meaningful difference in chosen primary endpoint between two treatment groups, *i.e.*, 20 point or 33% difference between two groups in mean LSOQ score reduction from baseline.

Inclusion/Exclusion Criteria

- Adult males and females scheduled to undergo first surgical intervention for a diagnosed unilateral herniation of lumbar intervertebral disc material associated with radiculopathy.
- Subjects entering Pivotal Study underwent period of at least 2 weeks of non-operative treatment without resolution of pain, unless surgeon decided subject was experiencing intractable pain, or there was substantial progression of loss of neurological function.

Inclusion Criteria

- Clinical signs and symptoms indicative of lumbar or lumbosacral radiculopathy, affecting one predominant nerve root level; Significant pain and symptoms measurable by LSOQ;
- Radiological evidence (MRI Study or CT/myelogram) of compression of a nerve root, and/or confirmed existence of an extruded or sequestered disc fragment, at a level compatible with clinical signs and symptoms;
- Compression of a nerve root, and/or confirmed existence of an extruded or sequestered disc fragment, at L4-L5 or L5-S1 level;
- Males, females of non-childbearing potential or females who were not pregnant (at time of enrollment) and agreed not to become pregnant for at least 30 days after surgery;
- Sexually active females of childbearing potential who agreed to use a medically acceptable method of contraception;
- 18 to 70 years of age;

Inclusion Criteria, Continued

- Laboratory test results within normal limits for following parameters:
  - Hematology;
  - Urinalysis;
  - Chemistry Panel

Exclusion Criteria

- Previous spinal surgery or chemonucleolysis at lumbar level;
- Treatment with any epidural steroids within 4 weeks prior to proposed surgery; Use of steroids perioperatively and/or intraoperatively;
- Presence of scoliosis; (> 10 degrees and considered by investigator to be clinically significant);
- Presence of foraminal stenosis;
- Known history of collagen-vascular or auto-immune disease (*e.g.*, rheumatoid arthritis, systemic lupus erythematosus), bleeding abnormalities, chronic debilitating disease, or malignancy within 5 years (except basal cell carcinoma);

Exclusion Criteria, Continued

- Myelogram or lumbar puncture for any reason within 24 hours prior to proposed surgery;
- Presence of any immunodeficiency disease, uncontrolled diabetes, or any systemic condition which, in surgeon's opinion, may influence the outcome of proposed surgery or postoperative period;
- History of analgesic abuse/addiction;
- Subject of a current or anticipated worker's compensation claim for any reason and/or party to a current or anticipated personal injury litigation for any reason;
- Participation in any other clinical study involving an investigational device or drug within the 30 days immediately preceding enrollment in Oxiplex/SP Gel Pivotal Study;
- Any known condition or circumstance, which would prevent completion of Pivotal Study or interfere with interpretation of Pivotal Study results.

Intraoperative Exclusions

- Subjects who met any of following criteria were not eligible for enrollment:
  - Dural entry during surgery;
  - Discovery of intraspinal tumor during surgery;
  - Required spinal fusion;
  - Multilevel herniation or the need to involve more than one level.

Surgical Protocol

- Standard posterior midline or paramedian approach;
- Remove some or all of disc from intervertebral location. Establish hemostasis and removal of hemostatic agents;
- Irrigate and aspirate prior to application of Oxiplex/SP gel in treated subjects and before closure in all subjects;
- Determine randomization assignment (Treatment group vs. Control group);

Surgical Protocol, Continued

- Treatment Group Only: Coat dura and exiting nerve root along both its dorsal and ventral surfaces. Apply gel into site of laminectomy/laminotomy to fill depth of surgical site to level of ventral surface of vertebral lamina. Volume delivered is not to exceed 3 mL.
- Gel implanted at L4-L5 or L5-S1.
- Close wound in routine fashion.

Clinical Evaluations

- Postoperative clinical evaluations performed at 1 mos (3-6 weeks) and 6 mos (22-28 weeks) by masked Clinical Evaluator (CE). Evaluations included:
  - Physical examination, including lumbar spine and lower extremities, motor/sensory function, and evaluation of wound site;
  - Assessment of AEs (assessed at all time points);
  - Review of laboratory test results for clinically significant changes (hematology and serum chemistries at 1 and 6 months; urinalysis at 1 month).

Clinical Evaluations, Continued

- For assessment of effectiveness, subjects completed LSOQ via phone (or mail) at 1, 3 and 6 mos
  - LSOQ: self-assessment questionnaire that served as Quality of Life instrument
- Interviewer and subject remained masked to study group assignment throughout study

Patient Demographics

	Oxiplex (n=177)	Control (n=175)
	Mean	Mean
Age	41.8	41.7
Height (cm)	173.0	172.5
Weight (kg)	86.0	83.8
Gender		
Male	87	98
Female	90	77
Race		
Caucasian	152	153
African American	9	4
Hispanic	8	11
Asian	2	3
Other	3	2

Safety Results
Analysis of AEs with Incidence ≥ 5%

Incidence occurring > 5 %	Oxiplex %		Control %	
Subjects Randomized	N=177		N=175	
Subjects Reporting Any Adverse Event	N=163		N=153	
Gastrointestinal Disorders				
Constipation	12	6.8%	6	3.4%
Nausea	35	19.8%	36	20.6%
Vomiting	10	5.6%	9	5.1%
General Disorders & Administrative Site Conditions				
Chills	8	4.5%	8	4.6%
Pyrexia	8	4.5%	11	6.3%
Injury, Poisoning, Procedural Complications				
Incision Site Complication	57	32.2%	69	39.4%
Procedural Pain	56	31.6%	54	30.9%

Incidence occurring > 5 %	Oxiplex %		Control %	
Subjects Randomized	N=177		N=175	
Subjects Reporting Any Adverse Event	N=163		N=153	
Musculoskeletal, Connective Tissue Disorders				
Arthralgia	12	6.8%	12	6.9%
Back Pain	44	24.9%	39	22.3%
Buttock Pain	12	6.8%	13	7.4%
Intervertebral Disc Protrusion	4	2.3%	9	5.1%
Muscle Spasm	25	14.1%	31	17.7%
Muscular Weakness	9	5.1%	9	5.1%
Musculoskeletal Stiffness	9	5.1%	5	2.9%
Myalgia	6	3.4%	13	7.4%
Pain in Extremity	26	14.7%	38	21.7%

Analysis of AEs with Incidence ≥ 5%, Continued

Incidence occurring > 5 %	Oxiplex %	Control %
Subjects Randomized	N=177	N=175
Subjects Reporting Any Adverse Event	N=163	N=153
Nervous System Disorder		
Dizziness	10 5.6%	8 4.6%
Headache	14 7.9%	12 6.9%
Hypoasthesia	18 10.2%	26 14.9%
Hyporeflexia	9 5.1%	4 2.3%
Sensory Loss	4 2.3%	8 4.6%
Psychiatric Disorders		
Insomnia	12 6.8%	7 4.0%
Skin and Subcutaneous Tissue Disorders		
Pruritis	8 4.5%	6 3.4%

Treatment-Emergent AEs

Relationship	Intensity	Subject	Postop Onset	Duration	Treatment Group	Comment
Definite — None	N/A					None.
Probable						
Nausea	Mild	*	Day of Surgery	Day of Surgery	Oxiplex	Spontaneous Resolution
Dizziness	Mild	*	Day of Surgery	Day of Surgery	Oxiplex	Spontaneous Resolution
Back Pain	Mild	*	Day of Surgery	1 week	Oxiplex	Spontaneous Resolution
Possible						
Difficult with Urinating	Moderate	**	6 Weeks	Ongoing	Oxiplex	Prostatitis
Low Back Pain	Severe	**	5 Weeks	8 Weeks	Oxiplex	Spontaneous Resolution
Recurrent HNP	Severe	**	4 Months	Ongoing	Oxiplex	Conservative Treatment
Delayed Wound Healing	Mild	**	4 Weeks	7 Weeks	Oxiplex	Retained Suture Removed

* Same Subject
** 4 Different Subjects

Serious Adverse Events (SAEs)

- 27 subjects (7.7%) experienced SAE
  - 13 SAEs (7.3%) in Oxiplex group
    - *e.g.* cellulitis, wound infection, incision site complication, headache, migraine, deep vein thrombosis
  - 14 SAEs (8%) in Control group
    - *e.g.* wound infection, CSF leakage, dural tear, hip fracture, nerve injury, spinal fusion surgery
- No SAE was categorized as definitely or probably related to device.

Re-operations

	P-value*	Oxiplex N (%)	Control N (%)
Subjects Randomized		177	175
Re-operation by 3-month	0.0665	1 (0.6%)	6 (3.4%)
Re-operation by 6-month**	0.0665	1 (0.6%)	6 (3.4%)

*P-value is for Oxiplex vs. Control and is from the Fisher's Exact test
**All re-operations occurred by 3 months following the primary surgery.

Other Secondary Safety Variables

- Oxiplex and Control groups comparable with respect to following variables:
  - Hematology
  - Chemistry
  - Urinalysis
  - Abnormal physical examination at 1-mos follow-up
  - Abnormal physical examination at 6-mos follow-up and post-operative neurology examination
- Balance in concomitant therapies received by Oxiplex and Control groups.

Effectiveness Results: Primary Endpoint

- FDA conducted an analysis of the primary effectiveness endpoint based on the original IDE model that showed that the difference of least squares means between the two groups was 0.1 on a 100-pt scale (p=0.96).

FDA Unadjusted Analyses on Leg Pain Improvement for CC

Visit	Oxiplex Leg Pain Improvement from Baseline Mean±Std (N[1])	Control Leg Pain Improvement from Baseline Mean±Std (N[1])	Oxiplex Improvement – Control Improvement = Treatment Effect (95% CI)	Unadjusted P-values for Treatment Effect (T-test[2])	Unadjusted P-values for Treatment Effect (Wilcoxon Rank Sum Test[3])
Baseline	67.5±15.2 (177)	67.7±14.1 (174)		0.90[4]	0.96[4]
Month 1	48.8±23.3 (165)	48.9±23.9 (160)	-0.1 (-5.3, 5.1)	0.97	0.97
Month 3	51.8±22.9 (168)	51.4±24.9 (162)	0.4 (-4.7, 5.6)	0.87	0.97
Month 6	51.7±23.8 (167)	50.7±25.3 (167)	0.9 (-4.4, 6.2)	0.74	0.88

1. Number of non-missing values.
2.T-test assumes leg pain improvement is normally distributed.
3. Wilcoxon Rank Sum test does not assume leg pain improvement is normally distributed.
4. These are the p-values for baseline leg pain scores comparisons.

(*Panel Question #5)*

FDA Analysis of Endpoints (6-month PMA CC)

Measures	Difference Of (Oxiplex-Control)	Control (N)	Oxiplex (N)	(95% Confidence interval)	Statistical significance
Leg Pain	0.91	167	167	(-4.38, 6.20)	No
Back Pain	2.32	167	167	(-3.37, 8.01)	No
Leg Weakness	0.10	167	167	(-0.10, 0.29)	No
Physical Symptoms	3.40	167	167	(-1.68, 8.48)	No
Patient Satisfaction	0.08	167	167	(-0.22, 0.38)	No
Disability Days	1.47	167	167	(-0.44, 3.38)	No
Activities of Daily Living Index	0.92	156	156	(-0.76, 2.59)	No

-This analysis was conducted by FDA, which showed slightly different results from the sponsor's analysis in the in-window population.
-Positive numbers indicate advantage of Oxiplex group.
-Completed Cases (PMA CC): 334 subjects who completed 6 mos post-surgical follow-up visit

OUS Experience

- CE Mark received in July 2001
- 6 post-market reports related to issues with device
  - Sponsor concluded reports were not attributable to use of device
- Prospective, subject blinded clinical study in China
  - October 2006-April 2007
  - 60 subjects, randomized 2:1 (Oxiplex: Control), 2 sites
  - Data collection and efficacy analysis ongoing

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P070023
Statistical Overview

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Orthopaedic and Rehabilitation Devices Panel Meeting
July 15, 2008

Outline

- Pivotal Study Design
  - Sample Size
  - History of Key Changes in Statistical Analysis Plan
- Subject Dispositions and Populations
- Comparability of Oxiplex and Control Subjects
- Analyses on Primary Effectiveness Endpoint
  - Overall Treatment Effect
  - Exploratory Subgroup Analyses
  - Site Variability
- Analyses on Secondary Effectiveness Endpoints
- Summary

Sample Size

- Sample Size Estimation:
  - Two Independent Normal Means with One Interim Analysis, $\delta=10$, $\sigma=32$, 15% loss of f/p
  - Originally 192 per Group, Interim Analysis Proposed at 33.3% Data
  - May 05 Changed the Interim Analysis to 75% Data, Sample Size to 394 for 334 Evaluable
  - Alpha Value 0.044 for Final Analysis
- Actual Enrolled:
  - 177 Oxiplex, 175 Controls for 352 Enrolled and 334 Evaluable at 6 months

Timeline of Key Changes in the Planned Statistical Analyses on the Primary Endpoint

- May 02 Protocol w/ Statistical Methods Conditionally Approved
  - Initial GEE model for the primary endpoint would contain treatment, time, baseline level and baseline level by treatment interaction term
  - Interaction term removed if not significant
- Aug 02 Enrollment Began
- Apr 06 Interim Analysis
- Dec 06 Revised Statistical Analysis Plan Submitted
  - All clinically relevant baseline factors would be screened
  - Interactions with treatment would be studied
- Aug 07 PMA Submission

Subject Dispositions at 6 Months and Subject Populations

	Oxiplex	Controls
Enrolled (ITT[1])	177	175
Died	0	1
Withdrawn/Terminated	1	2
Lost to Follow-up	5	4
Far beyond visit Window[2]	4	1
"Completed Cases" (PMA CC)	**167**	**167**
6-month In-window Population	145	141

1. One control subject was unblinded and excluded from the ITT population by the Sponsor.
2. Five subjects had 6-month visit far beyond the visit window (> 365 days), and were excluded from the "Complete Cases" by the sponsor.

Comparability of Oxiplex Subjects and Control Subjects

	Control (N=175)[1]	Oxiplex (N=177)	P-value[2]
Age			
Mean (SD)	41.7 (10.7)	41.8 (10.5)	0.93
Gender (Male)	98 (56.0%)	87 (49.2%)	0.20
Body Mass Index			
Mean (SD)	27.8 (5.6)	28.4 (5.8)	0.25
Baseline Leg Pain			
Mean (SD)	67.7 (14.1)	67.5 (15.2)	0.90
Baseline Back Pain			
Mean (SD)	59.4 (21.8)	59.2 (20.9)	0.90

1. One control patient had missing baseline leg pain and back pain scores and was unblinded following surgery.
2. Not adjusted for multiplicity. T-test for continuous variables, Fisher's exact test for categorical variables.

Primary Effectiveness Endpoint

- Improvement in Leg Pain Measured by LSOQ at 1, 3 and 6 months post surgery
- Converted to 0-100 Scale
- Analyzed with GEE model
- In ITT (primary) and CC (supportive) population
  - Overall Treatment Effect
  - Exploratory Subgroup Analyses
  - Site Variability

Model (Covariate) Selection

- Why Statistical Models?
  - To adjust for possible covariate imbalance between arms
- Model Selection Methods
  - Pre-specified covariates
  - Automated covariate selection by software (with pre-specified rules)
  - Combination of pre-specified covariates and automated selection
- (Pre-specified) Treatment-by-covariate Interactions Added Last

Sponsor's Model Selection Process

- Unusual
- Screens Treatment-by-covariate Interactions Early
- Manual Backward Selection Process
  - Difficult to Replicate
  - Prone to Biases
- Complex Model
- Difficult to Interpret

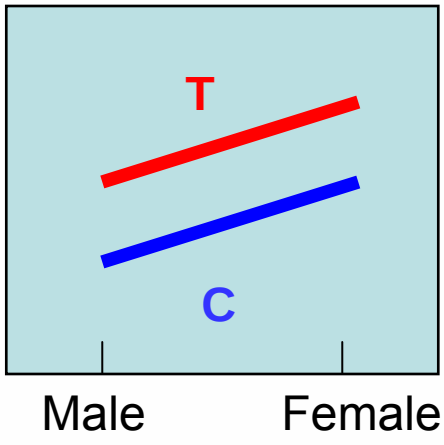
The Sponsor's GEE Model (PMA CC)

- Ten Covariates
  - Site, baseline leg pain, back pain, functional score, cpt, pulmonary abnormality, three neurosensory exam results, sexual function
- Five Treatment-by-covariate Two-way Interactions
  - Treatment by baseline back pain, pulmonary abnormality, two neurosensory exam results, sexual function
- Overall Treatment Effect Difficult to Characterize
  - P-value for main treatment effect should not be used when interaction present

(Panel Question #4)

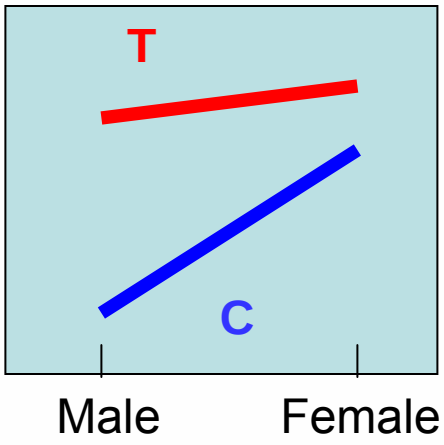
Hypothetical Example: Treatment-by-gender Interaction

Overall Trt Effect
No Interaction



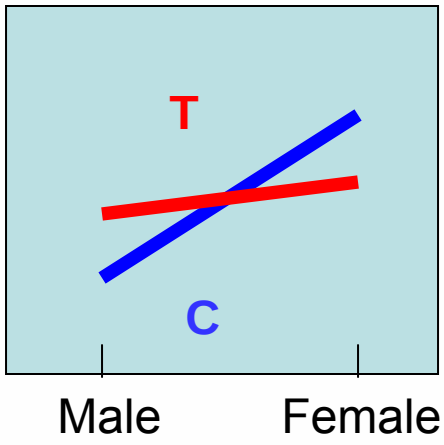
A

Overall Trt Effect
Quantitative Interaction



B

No Overall Trt Effect
Qualitative Interaction



C

Treatment-by-covariate Interactions

- Allows different treatment effect for different subgroups
- Usually first step towards subgroup analyses
- Exploratory if not pre-specified
- Model more complex
- Overall treatment effect difficult to characterize

FDA's GEE Models for Primary Effectiveness Endpoint

- Model 1 – Derived from Sponsor's Model (PMA CC) without the Interaction Terms
- Model 2 – IDE Model with Treatment, Visit and Baseline Leg Pain (Treatment-by-baseline Leg Pain Not Significant)

FDA's Results from Primary Endpoint Models (PMA CC Population)

	Adjusted Overall Trt Effect[1]	95% Confidence Interval	P-value for Overall Trt Effect
Model 1	1.8	(-1.5, 5.1)	0.29
Model 2	0.1	(-3.6, 3.8)	0.96

1. Difference in leg pain reduction at 1, 3 or 6 months on 0-100 scale

Primary Effectiveness Endpoint – FDA Unadjusted Analysis (PMA CC Population)

Visit	Leg Pain Improvement from Baseline Mean±Std (N[1])		Oxiplex Improvement – Control Improvement = Treatment Effect (95% CI)	P-values for Treatment Effect[2]
	Oxiplex	Control		
Month 1	48.8±23.3 (165)	48.9±23.9 (160)	-0.1 (-5.3, 5.1)	0.97
Month 3	51.8±22.9 (168)	51.4±24.9 (162)	0.4 (-4.7, 5.6)	0.87
Month 6	51.7±23.8 (167)	50.7±25.3 (167)	0.9 (-4.4, 6.2)	0.74

1. Number of non-missing values
2. From t-test, not adjusted for multiplicity

Treatment-by-covariate Interactions Screened by Sponsor

- Trt-by-age
- Trt-by-weight
- Trt-by-BMI
- Trt-by-baseline leg pain
- Trt-by-baseline back pain
- Trt-by-baseline function pain
- Trt-by-baseline symptom score
- Trt-by-gender
- Trt-by-site
- Trt-by-surgical time
- Trt-by-cpt
- Trt-by-operation level
- Trt-by-leg weakness
- Trt-by-history of eye, ENT abnormality
- Trt-by-history of dematological abnormality
- Trt-by-history of cardiovascular abnormality
- Trt-by-history of pulmonary abnormality
- Trt-by-history of gastrointestinal abnormality
- Trt-by-history of musculoskeletal abnormality
- Trt-by-history of genitourinary abnormality
- Trt-by-history of renal abnormality
- Trt-by-history of hematologic/immunologic abnormality
- Trt-by-history of psychosocial abnormality
- Trt-by-history of neurological abnormality
- Trt-by-history of endocrine/metabolic abnormality
- Trt-by-history of surgical/Trauma (<=10 years)
- Trt-by-history of psychological abnormality
- Trt-by-history of allergies
- Trt-by-clinical presentation
- Trt-by-l4rt (neurosensory exam)
- Trt-by-l5rt (neurosensory exam)
- Trt-by-s1rt (neurosensory exam)
- Trt-by-l4lt (neurosensory exam)
- Trt-by-l5lt (neurosensory exam)
- Trt-by-s1lt (neurosensory exam)
- Trt-by-slr
- Trt-by-gait
- Trt-by-sexual function
- Trt-by-RILIO (Right Iliopsoas Neuromotor Exam)
- Trt-by-RQUAD (Right Quadriceps Neuromotor Exam)
- Trt-by-RANT (Right Anterior Tibialis Neuromotor Exam)
- Trt-by-RGAST (Right Gastronemius Neuromotor Exam)
- Trt-by-REXT (Right Extensor Hallucis Longus Neuromotor Exam)
- Trt-by-LILIO (Left Quadriceps Neuromotor Exam)
- Trt-by-LQUAD (Left Quadriceps Neuromotor Exam)
- Trt-by-LANT (Left Anterior Tibialis Neuromotor Exam)
- Trt-by-LGAST (Left Gastronemius Neuromotor Exam)
- Trt-by-LEXT (Left Extensor Hallucis Longus Neuromotor Exam)

FDA Exploratory Subgroup Analysis (PMA CC Population[1])

Baseline Back Pain	Visit	Leg Pain Improvement from Baseline Mean (N[2])		Treatment Effect (95% CI)	P-values for Treatment Effect[3]
		Oxiplex	Control		
< 63	Month 1	40.9 (78)	42.4 (70)	-1.5 (-8.4, 5.3)	0.66
	Month 3	42.7 (82)	44.2 (71)	-1.5 (-8.4, 5.5)	0.68
	Month 6	43.1 (79)	47.2 (70)	-4.1 (-11.1, 2.9)	0.25
>= 63	Month 1	55.9 (87)	53.9 (90)	2.0 (-5.2, 9.1)	0.59
	Month 3	60.5 (86)	57.0 (91)	3.5 (-3.5, 10.5)	0.32
	Month 6	59.3 (88)	53.3 (97)	6.0 (-1.4, 13.4)	0.11

1. This Analysis was conducted by FDA for the PMA CC population, which may show different results from the sponsor's analysis in the in-window population
2. Number of non-missing values
3. From t-test, not adjusted for multiplicity

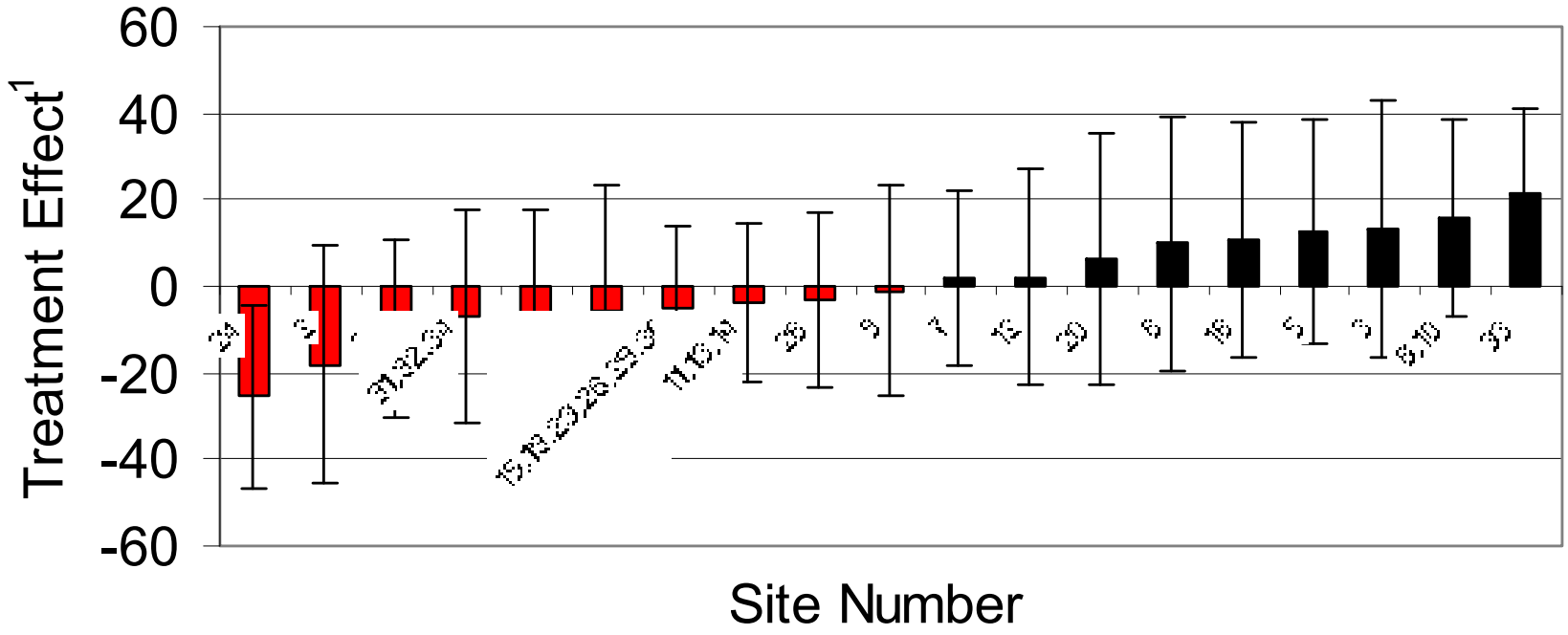
(Panel Question #6)

Site Variability

- Tested by Treatment-by-site Interaction
- FDA Model 1
  - Remove All Five Interaction Terms from Sponsor's GEE Model
  - Add Trt-by-site Interaction
  - P-value = 0.030 for Trt-by-site Interaction
- FDA Model 2
  - Add Site and Trt-by-site Interaction to IDE Model
  - P-value = 0.010 for Trt-by-site Interaction
- Site Variability Existed

Site Variability

Difference in 6-month Leg Pain Improvement
between Oxiplex and Control by Site



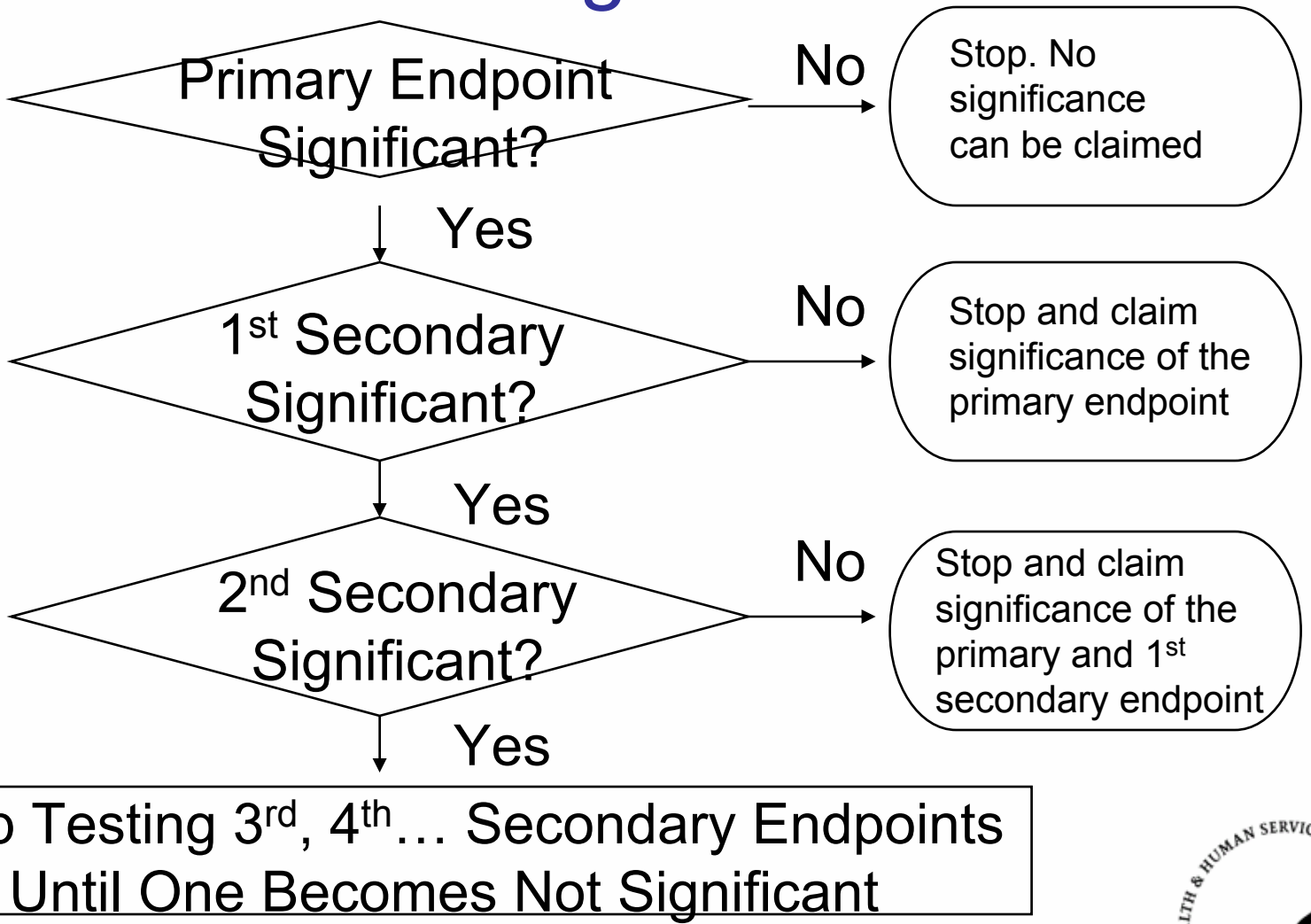
1. Positive treatment effect indicates advantage of Oxiplex Group

(Panel Question #3)

Secondary Effectiveness Endpoints

- Hierarchical Closed Testing Procedure
- Proposal Conditionally Approved in 12/06
- Sequential Testing of Back Pain, Lower Extremity Weakness, Physical Symptoms, Patient Satisfaction, Disability Days and Activities of Daily Living

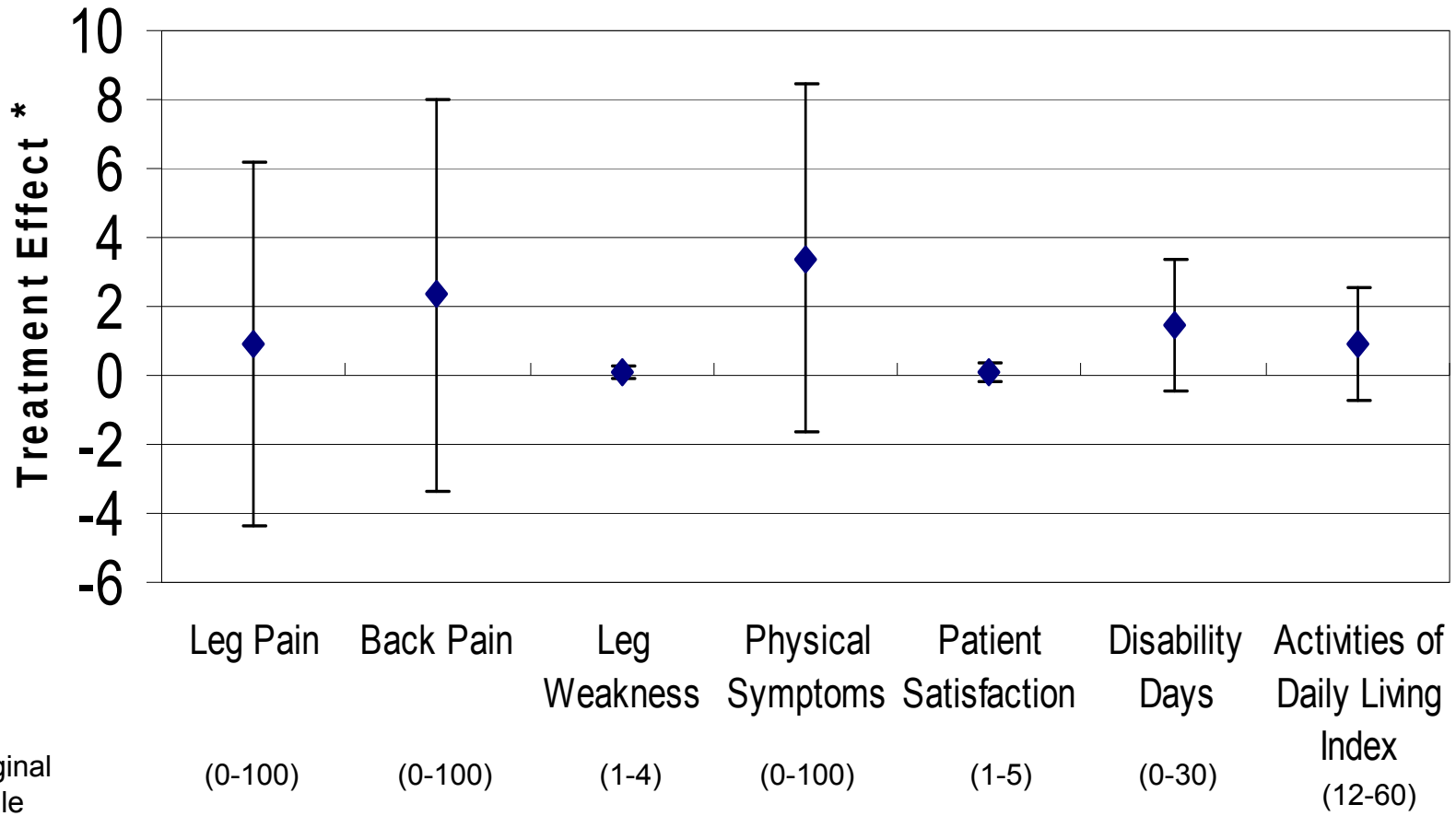
FDA's Understanding of a Hierarchical Closed Testing Procedure



FDA's Assessment of Secondary Effectiveness Endpoint Analyses

- According to hierarchical closed testing procedure, this analyses should not have been performed
- Similar to primary effectiveness endpoint analyses
- Unusual model selection processes
- Complex GEE Models with multiple treatment-by-covariate interactions
- Difficult to characterize overall treatment effects of secondary endpoints
- Subsequent exploratory subgroup analyses

FDA Unadjusted Analysis – All Effectiveness Endpoints at 6-month (PMA CC Population)



* Difference between Oxiplex and Control. Positive treatment effect indicates advantage of Oxiplex

Summary

- Primary Effectiveness Endpoint (PMA CC)
  - Overall treatment effect was not significant based on FDA's analysis
  - Subgroup analyses were exploratory
  - Site variability may exist
- Secondary Effectiveness Endpoints (PMA CC)
  - None significant at 6 months based on FDA's analysis

FDA Presentation

- Introduction
- Summary of Non-Clinical/Pre-Clinical Studies
- Clinical Study
- Statistical Overview
- Post-Approval Study
- Panel Questions

P070023
Oxiplex/SP Gel
Post-Approval Study (PAS)

Jiping Chen, MD, PhD, MPH
Epidemiology Branch
Division of Postmarket Surveillance
Office of Surveillance and Biometrics

Orthopaedic and Rehabilitation Devices Panel Meeting
July 15, 2008

Outline

- General principles
- Rationale for postmarket questions
- Proposed Post-Approval Study (PAS) outline
- Assessment of the PAS outline
- PAS issues for panel discussion

Reminder

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable.

- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.

- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.

General Principles for Post-Approval Studies

- Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable evidence of device safety and effectiveness.
- Post-approval studies should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

Need for Post-Approval Studies

- Gather postmarket information
  - Longer-term performance
  - Real world community performance
  - Effectiveness of training programs
  - Sub-group performance
  - Rare adverse events

- Account for Panel recommendations

Important Postmarket Questions

- What will the real world performance of the device be in the more general population of patients and providers?

- What is the long-term safety and effectiveness of the device postmarket?

Overview of Sponsor's PAS Outline

Study Objective	To confirm the safety and reduction in disability days in subjects who receive Oxiplex during first-time lumbar disc surgery
Study Design	Prospective, multi-center cohort, non-inferiority design with historical controls
Population and Sample Size	Oxiplex PAS Group: subjects who will be treated with Oxiplex in the PAS (N = 210) Historical Controls: Oxiplex-treated subjects in the pivotal study who completed 6-month follow-up (N = 145)
Follow-up	6-month postoperative office visit

Overview of Sponsor's PAS Outline (Cont'd)

Effectiveness Endpoint	Reduction in **disability days** that occur over the last 30 days of the 6-month period after surgery
Hypothesis	the mean reduction in disability days for the last 30 days of the 6- month period in subjects who will receive Oxiplex is no worse than Oxiplex-treated subjects in the pivotal study (reduction in disability days) by a margin of 2.5 days (~33%).
Safety Endpoints	Descriptive analysis (AEs by type and overall with rates and 95% CIs): ▪ Procedure- and device-related AEs ▪ Number of re-operations; and ▪ Musculoskeletal and lower extremity neurological function

Sponsor's PAS Outline
FDA Assessment

Study Design

- Non-inferiority design with historical controls
  - Patient comparability: PAS Oxiplex-treated group *vs.* Oxiplex-treated subjects in the pivotal study

- Non-inferiority margin (δ) for the primary endpoint
  - The appropriateness of the margin (2.5 days = ~ 33% of the pivotal study reduction)
  - Lack of clinical justification
  - "*3.5 times lower than the standard deviations* " not clear
  - The same standard deviation not applicable to both groups

Sponsor's PAS Outline
FDA Assessment (cont'd)

Effectiveness Endpoint

The reduction in disability days that occurs over the last 30 days of the 6-month period after surgery

- Lack of justification for not using mean changes from baseline in leg pain as the primary endpoint
- Testing the statistical significance of the difference in the secondary effectiveness endpoints when the difference in the primary endpoint is not significant

Sponsor's PAS Outline
FDA Assessment (cont'd)

Safety Endpoints

Procedure- and device-related AEs ONLY

- An underestimation of AEs

Sponsor's PAS Outline
FDA Assessment (cont'd)

Duration of follow-up

Subjected will be followed for 6 months post surgery

- Literature: AEs (e.g. Intervertebral disc protrusion) may occur with scars within 12 month after surgery
- Postmarket: An AE report analysis with other CMC-based adhesion barrier indicated ~ 8% AEs occurred beyond 6 months

Sponsor's PAS Outline
FDA Assessment (cont'd)

Study sample size

- N=355 [210 PAS Oxiplex subjects (156 evaluable subjects), 145 pivotal Oxiplex subjects]
- 25% drop-off rate
  - Mean 7.67 reduction in disability days in pivotal Oxiplex subjects, PAS subjects have similar value (0 in difference)
  - Non-inferiority margin of 2.5 days
  - One -sided test at alpha 0.05
  - 145 pivotal Oxiplex subjects

- Sample size = 154 for PAS Oxiplex subjects
- Develop a better plan to minimize loss to follow-up
- Lack of measures to be taken if the number of subjects falls below 355 during follow-up

PAS Issues for Panel Discussion

1. Study Objective/Question

Planned: To confirm device safety, and reduction in disability days, in subjects who receive Oxiplex during first-time lumbar disc surgery

Issue:

- Appropriateness of the objective/question to be studied in a PAS to address device long-term safety/effectiveness

PAS Issues for Panel Discussion

2. Study Design

Planned: Non-inferiority design to compare the reduction in disability days in PAS Oxiplex-treated patients *vs.* the Oxiplex-treated patients in the pivotal study

Issue:

- Appropriateness of the study design to address device long-term safety/effectiveness
- Appropriateness of the non-inferiority margin (2.5 days)

PAS Issues for Panel Discussion

3. Control Selection

Planned: Oxiplex-treated PAS population *vs.* Oxiplex-treated subjects in pivotal study (historical controls)

Issue:

- Appropriateness of the study population to address device safety/effectiveness postmarket

PAS Issues for Panel Discussion

4. Effectiveness Endpoint

Planned: The reduction in disability days that occur over the last 30 days of the 6-month period after surgery

Issue:

- Appropriateness of the endpoint to address device long-term effectiveness

PAS Issues for Panel Discussion

5. Duration of Follow-up

Planned: 6 months of follow-up

Issue:

- Optimal duration of follow-up to address device safety/effectiveness postmarket

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Questions?